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Review Article

Microchimerism: covert genetics?

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Abstract: While the world of genetics has been dominated over the last decade by technological advances allowing the identification of common variants underlying the major complex diseases, it is increasingly clear that other genetic mechanisms are also involved in genetic susceptibility and resistance to disease. One understudied contender is microchimerism (maternal and foetal), resulting from bi-directional transfer of cells across the placental barrier in pregnancy. Data from several diseases suggest that elevated levels of microchimerism are associated with autoimmunity. Theories differ however on the role of these cells in the disease process. Some suggest that they increase genetic susceptibility while others suggest that these cells are effectors of the immune response, or that they represent the target of the immune response while another proposes that elevated levels in disease are caused by ongoing repair of damaged tissue. Intriguingly these semi allogeneic cells are tolerated in healthy individuals, albeit at a lower level than in disease scenarios and recent studies in cancer suggest that foetal microchimeric cells may provide surveillance and repair. Many questions remain to be answered about this new avenue of genetics. It is likely that as technology advances our understanding of, and ability to manipulate these cells for therapeutic gain, will push forward new frontiers in medicine.

Keywords: Foetal microchimerism, maternal microchimerism, autoimmune diseases

Introduction

Microchimerism, the co-existence of a small number of cells which originate from a genetically distinctive individual often results from bone marrow transplantation where donor cells can be detected in recipient tissues (reviewed in [1]). It has recently become clear however that more common forms of microchimerism exist, namely, maternal and foetal microchimerism resulting from the bi-directional transfer of cells in pregnancy. The engraftment of maternal cells in the foetus is known as maternal microchimerism (MMc) while cell transfer in the opposite direction called foetal microchimerism (FMc) (Figure 1).

The phenomenon of maternal microchimerism

was initially recognized in children with severe combined immunodeficiency more than 20 years ago [2] and maternal cells were identified in umbilical cord blood samples from male infants in 1995 [3]. The placenta is therefore not an impenetrable barrier to cellular traffic. It has been shown that microchimeric cells persist for many years in healthy individuals; foetal cells have been found in maternal blood up to 27 years postpartum [4] and maternal cells have been detected in her offspring for up to 49 years [5].

The maternal immune system was initially shown to be exposed to foetal microchimeric cells at 15-27 weeks gestation [6] and subsequently even as early as 5-6 weeks gestation [7]. Foetal DNA has been detected in both the

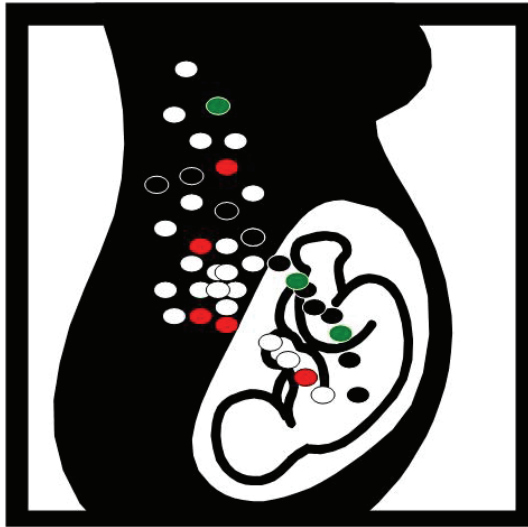


Figure 1. Schematic diagram of a pregnant woman with transfer of foetal cells (white) to the mother and maternal cells (black) to the foetus. Maternal stem cells are red while foetal stem cells are green.

cellular and cell-free compartments of maternal blood beginning at 7-16 weeks but rising after 24 weeks and reaching a peak at birth [8]. After birth it has been found that the levels of foetal microchimeric cells are significantly higher than that of maternal microchimeric cells [9, 10].

In genetics, detection of fetal DNA in maternal blood has had greatest relevance in prenatal diagnosis where early non-invasive prenatal testing for cell free fetal DNA in maternal blood has translated into clinical practice for some genetic traits (reviewed in Wright and Chitty *BMJ* 2009) [11]. Microchimeric cells have however potentially much broader relevance including the induction and maintenance of immune tolerance to genetically distinct (allogeneic) cells; contributing to susceptibility and resistance to disease, especially autoimmune disease and possibly also to tissue repair.

Most studies of microchimerism have focused on analysis of haematopoietic cells but it is increasingly clear from human [12, 13] and animal [14] studies that microchimeric cells also exist in other tissues including the liver, heart and brain supporting the thesis that some cells that cross the placental barrier in each direction are stem cells with multilineage potential [15,16].

Study of microchimerism has been restricted

over the past two decades by technological limitations in studying rare event cells. Studies of microchimerism in humans have been limited to: 1) Genetic epidemiological studies of the frequency of non-inherited maternal alleles (NIMA) in affected compared to control individuals. These studies require large well characterized patient populations to generate robust associations. 2) Quantitative PCR analysis of the level of the NIMA in disease versus health. 3) Detection of the Y chromosome by PCR in maternal DNA and 4) Direct detection and quantification of female cells in autopsy tissue sections from male offspring (and male cells in maternal tissue) by fluorescence in situ hybridization (FISH) with concomitant cellular phenotyping by immunohistochemistry.

More recently animal models of microchimerism have been developed which tag maternal or foetal cells with for instance green fluorescent protein (GFP) allowing MMC to be followed [17]

Pregnancy is, by definition, a period of immune privilege and it is well established that the balance of immune mediators promotes maintenance of the foetal "graft". The persistence of maternal cells implies that her offspring is tolerant to a low level of genetically distinct antigen. The mechanism underlying this naturally obtained tolerance is unknown but is supported by the observation of improved survival of renal transplants from sibling donors who share the non-inherited maternal HLA with the recipient [18]. Increased levels of microchimerism, both foetal and maternal, have however also been associated with autoimmunity.

Microchimerism in autoimmunity

Although microchimeric cells exist in very low numbers in healthy individuals, it has been suggested that they are involved in the pathogenesis of autoimmune diseases. Interestingly autoimmune diseases are more common in women than men and most commonly develop in women of childbearing age or older.

Chronic graft-versus-host disease (cGvHD), a common complication of bone marrow transplantation has clinical similarities to some autoimmune diseases (including the development of autoantibodies) i.e. Sjögren syndrome and Systemic Sclerosis [19]. Susceptibility to cGvHD is associated with incompatibility between the HLA genes expressed by the "invading" population

from the donor and those of the recipient. Given that most autoimmune diseases like rheumatoid arthritis and type 1 diabetes occur in subgroups of the population carrying certain HLA genes it is reasonable to argue that HLA "incompatible" alleles from the invading microchimeric population may cause a similar reaction in these genetically susceptible individuals. This might suggest that microchimerism resulting from transplantation and microchimerism resulting from pregnancy have similar mechanisms by which they influence the immune system.

In this review, studies suggesting that the role of microchimeric cells in disease can be either beneficial or detrimental will be discussed:

Foetal microchimerism in autoimmune diseases

Systemic sclerosis (SSc)

Systemic sclerosis (also called scleroderma) is clinically heterogeneous, chronic immunological disorder characterized by increased collagen deposition in the skin and various internal organs and is associated with a cellular infiltrate consisting primarily of T lymphocytes. A role for fetal microchimerism in SSc was first reported by Nelson et al. in 1998 [20] when women with systemic sclerosis had significantly higher levels of male DNA, as detected by Y chromosome specific PCR, than controls. Several subsequent studies from this group and others have replicated this observation and revealed that FMc in SSc patients are CD3⁺, CD4⁺ and CD8⁺ T lymphocytes with populations enriched in CD4⁺ subset, and they express CD25⁺ T cell activation marker [21, 22].

Autoimmune thyroiditis

Hyperthyroidism (Graves' disease) and hypothyroidism (Hashimoto's thyroiditis) are generally considered to be most prevalent in middle aged females particularly those who have had children and nearly two thirds of newly diagnosed Graves' disease cases in women with children occur within one year of delivery [23].

Several studies have shown that FMc was more frequent in thyroid tissue from patients with Hashimoto's thyroiditis and Grave's disease compared to control tissue [24, 25, 26, 27]. In cases where attempts have been made to phenotype the FMc, they have been described as

expressing epithelial [25] and lymphocyte markers [27].

These data are complemented by observations in a mouse model of autoimmune thyroiditis where FMc was identified in 12 of 26 mice with autoimmunity compared to 2 of 10 controls. In this study the fetal cells had an immune cell phenotype (T cells and dendritic cells) [28].

Systemic lupus erythematosus (SLE)

Healthy women with no history of autoimmune disease and women diagnosed with systemic lupus erythematosus (SLE) were studied to ascertain levels of foetal microchimeric cells. Both groups of women had previously given birth to at least one son. DNA was extracted from PBMCs and quantitative real time PCR of the SRY locus on the Y chromosome was used to measure levels of male foetal DNA. Levels of FMc in women with SLE were significantly higher than healthy control women ($P = 0.034$; $OR = 4.22$) [29]. Interestingly in this study it was also found that, although not statistically significant, levels of foetal microchimeric cells were higher in mothers with older sons suggesting time since the delivery is directly proportional to levels of foetal microchimerism. The authors speculate that this observation suggests that a foetal cell lines become established over time. The number of subjects analysed in this study was however relatively small (18 healthy control women compared to 28 women suffering from SLE).

Rheumatoid arthritis

It has been reported that approximately 75-90% of mothers that suffer from rheumatoid arthritis (RA) found that their symptoms improve spontaneously during the second or third trimester of pregnancy, but return within 3-4 months after delivery [30, 31, 32]. The explanation for this effect remains unknown, but it has been proposed that HLA-DR and DQ antigen incompatibility between mother and child suppresses the maternal immune system during pregnancy and RA improves [33]. Indeed a study of serum foetal DNA levels showed an association with disease activity in pregnant women with RA [34].

Foetal Microchimerism and cancer

A recent focus of studies of microchimerism is cancer. FMc were identified in 50% of papillary

thyroid tumors by Srivarsa et al. [12] while FMc positive for the lymphocytic marker, CD45, were detected in papillary thyroid cancer in 2008 by Cirello and colleagues [35]. When DNA was extracted from peripheral blood from 99 parous women, 54 with primary invasive breast cancer and 45 general population controls. Women harboring FMc were less likely to have had breast cancer ($p = 0.02$) and FMc concentrations were higher in controls versus cases ($p = 0.01$) [36]. In a larger case-control follow up [37] the same researchers replicated their observation and hypothesized that parous women with breast cancer fail to harbor a potential source of naturally acquired allogeneic immunity. Further research is required to characterize this potentially protective subset of FMc.

Maternal microchimerism in autoimmune diseases

Systemic sclerosis

Foetal microchimerism has been associated with SSc, as described above, but there are also data supporting a role for MMc in this condition. Long-term persistent MMc have been discovered in the peripheral blood of SSc patients as well as healthy controls up to 49 years of age [5]. Quantitative PCR revealed that MMc occurred more frequently among women with SSc (72%) compared to healthy controls (22%) (Odds ratio 9.3, $P=0.001$), but the levels of MMc (expressed as genome equivalent of maternal cells per million, gEq/mil) were not significantly different (0-68.6 gEq/mil in SSc patients, 0-54.5 in healthy women) [38]. Additional analysis of MMc levels in bone marrow and in multiple tissues from a patient who died of SSc strikingly showed that even if absent in the peripheral blood, significantly high levels of MMc could still be detected in lung, heart, spleen, and in pancreas while 10-20-fold lower levels were observed in bone marrow and gut [38]. Both FMc and MMc can therefore be detected in SSc patients and are thought to contribute to SSc aetiology. However, whether MMc function similarly or differently to FMcs, what immune challenges they present to the host are still unclear.

Neonatal lupus syndrome

Neonatal lupus syndrome (NLS) occurs *in utero*. Infants born to mothers with anti-Ro and anti-La antibodies have a high risk of developing NLS,

resulting in severe inflammation including congenital heart block. Employing a fluorescent *in situ* hybridisation (FISH) assay, MMc were detected in 15 of 15 sections of NLS heart tissue, and their frequencies ranged from 0.025% to 2.2% of total cells. By contrast, maternal cells were found in only 2 of 8 control sections (0-0.1% of total cells). Subsequent immunohistochemistry assay showed that only very few of these MMc expressed hematopoietic marker CD45, yet 86% of them expressed sarcomeric alpha-actin (a specific marker for cardiac myocytes) [13]. These data indicate that MMc in neonatal somatic tissue represent differentiated tissue-specific cells which may be targeted by host immune system.

Juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is a multisystem autoimmune disease that results from inflammation of the small vessels of the muscle, skin, gastro-intestinal tract and other organs. Involvement of the immune system in JDM has been demonstrated by the presence of lymphocytic and phagocytic infiltrates in muscle biopsies from children with JDM [39] and association with the human leucocyte antigen (HLA) class II allele DQA1 *0501 [40]. Recent studies investigated maternal microchimerism in JDM [41, 42, 43]. Maternally derived chimeric cells were shown to be present more often in muscle biopsies from children with JDM compared to controls. Analysis of whole blood DNA by qPCR demonstrated increased MMc in children with JDM compared to their healthy siblings. Further, in unrelated healthy offspring the presence of chimerism was shown to be associated with HLA genotype of the mother, in particular HLA DQA1*0501 [43]. Experiments on peripheral blood lymphocytes showed that maternally derived microchimeric cells are activated when exposed to the JDM child's lymphocytes indicating that MMcs are immunologically active and may play a direct role in the disease process.

Type 1 Diabetes

Type 1 Diabetes (T1D) is characterized by insulin deficiency resulting from autoimmune destruction of insulin secreting islet beta cells with lymphocytic and macrophage infiltration of the pancreas.

Using qPCR to detect the non-inherited mater-

nal HLA allele in peripheral blood DNA, MMC were shown to be present in higher levels in 94 individuals with T1D compared to 54 unaffected siblings and 24 unrelated healthy subjects [44]. Employing a FISH assay to detect MMC in pancreatic tissue from a patient with T1D compared to healthy controls with concomitant immunohistochemistry to stain for insulin and CD45 (a marker for haematopoietic cells), insulin staining, presumed beta cells were observed at higher levels in the T1D pancreas. Only very few of the maternal cells in the pancreas stained for CD45, indicating that it is unlikely that MMC act as effectors in the autoimmune response in T1D although further studies are necessary to independently replicate this observation. Nelson et al suggested that increased levels of insulin staining MMC in T1D pancreas may suggest that these cells play a role in the repair of damaged tissue. Further studies have confirmed the presence of maternal cells in T1D pancreas (**Figure 2**) that stain positively for insulin but more detailed phenotyping is required to define the role of MMC in the pancreas.

Microchimerism and genetic disease

The frequency of microchimerism appears to be increased when foetal cytogenetic abnormali-

ties occur. In a study by Bianchi et al [45] the mean number of male foetal cells present in the mother when the foetus has Down's syndrome was elevated 6-fold compared to women with normal male foetuses and in the study by Srivatsa et al. [12] of maternal microchimerism in newborn tissues, MMC levels were highest in the thymus of a child with Down's syndrome and non-immune hydrops. One potential explanation therefore of the intriguing epidemiological observation that risk of Alzheimer's disease (AD) is increased in the mothers of children with Down's Syndrome [47] could be engraftment of foetal DS cells in the maternal brain. There is however, as yet, no proof for this hypothesis.

The Future of Microchimerism

As represented in **Figure 3** microchimeric cells, both foetal and maternal have been identified in a variety of tissues with differing phenotypes. Depending on the disease scenario data have been generated to support a variety of hypotheses: it is possible that MMC are 1. effectors of the immune response 2. targets of the immune response or indeed 3. beneficial with regard to tissue repair and cancer recognition. More evidence is needed to clarify the role of microchimeric cells in autoimmunity and cancer. This

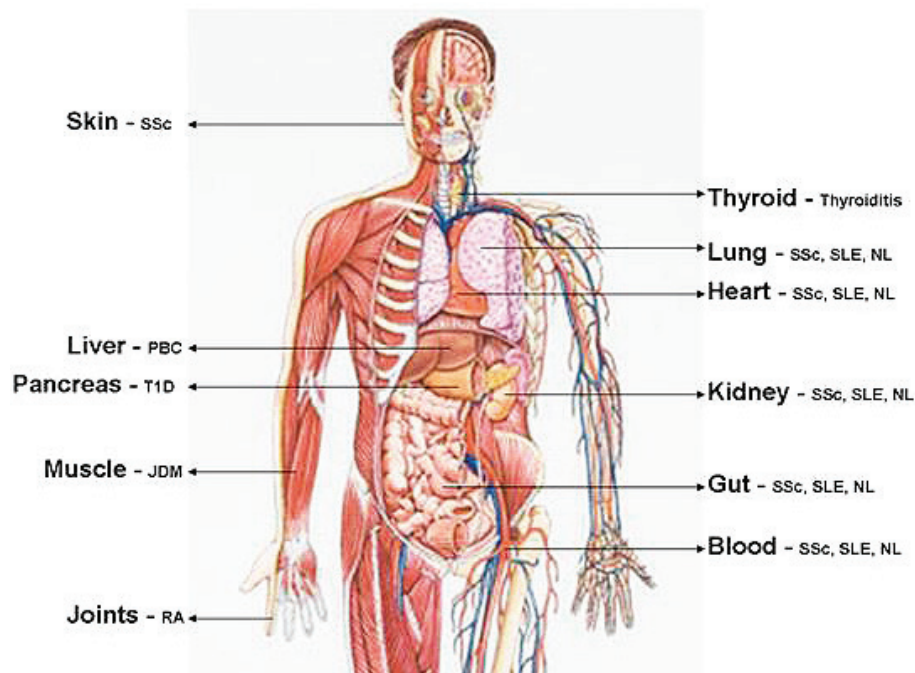


Figure 2. Some organs where microchimeric cells have been associated with autoimmunity.

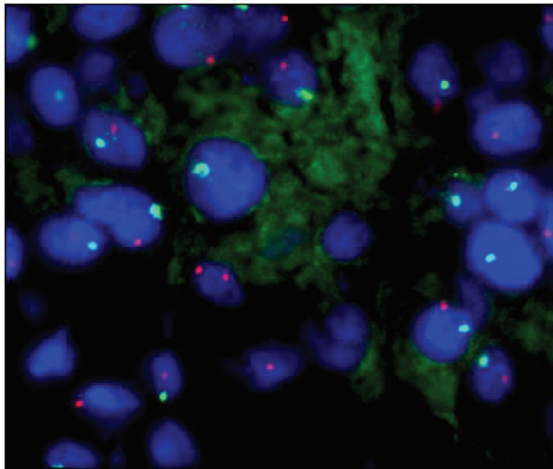


Figure 3. A maternal cell in human pancreas. The X chromosome is indicated by a red dot, the Y chromosome by a light green dot and insulin staining in dark green.

area of research is largely operating at the limitations of technical capability: Microchimerism is currently detected largely using two strategies: 1. using qPCR either for the non-shared, non-inherited maternal allele when maternal genotyping is available or for the presence of Y markers in female tissue or 2. Detection of female cells in male tissue or male cells in female tissue. As biological techniques become more sophisticated it should be possible to phenotype MMc in tissue sections more easily allowing definitive analysis of microchimeric cells and strategies to either target or enhance microchimeric cells for therapeutic benefit as appropriate.

Although steady developments in the field of microchimerism have occurred over the last two decades, this is effectively a new field which has been hampered by the complexity of the techniques required to analyse these rare cells in detail. Emerging technologies such as the ability to isolate and analyse individual microchimeric cells by laser capture microscopy will provide new insights into whether microchimerism is simply natural physiology or natural physiology with the capacity to contribute to our understanding of disease mechanisms as well as cellular differentiation and repair.

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